REMARKS

The Amendments to the Specification

The amendment to the title is believed to more clearly state the subject matter claimed in the present application.

The Claim Amendments

Claims 272, 273, 280-284, 288, and 291 were pending in the application and were examined. Claim 288, which has been withdrawn by the USPTO, stands canceled in the present amendment without acquiescence to any rejections and without prejudice to the prosecution of its subject matter in related divisional, continuation, and continuation-in-part applications. Claims 272, 273, 280-284, and 291 stand rejected.

Claims 272, 273, 280, and 291 stand amended in the present Amendment.

In general, support for the amendments is found in the description of eye abnormalities (e.g., pages 63-64) and in the description of the knock-out mice and the phenotype exhibited by (+/-) and (-/-) knock-out mice (e.g., pages 162-164). Applicants disclose that the gene encoding the PRO224 polypeptide was disrupted in the knock-out mice; that PRO224 is a member of the family of low-density lipoprotein (LDL) receptors, class A; and that it is known that LDL receptors play an important role in cholesterol metabolism (page 162, lines 20-21 and 31-32). Applicants observed an increased mean artery-to-vein (A/V) ratio in both (-/-) and (+/-) PRO224-knockout mice, and that this observation indicated retinal degeneration (page 164, lines 11-12). Applicants further disclosed that "[s]uch detected retinal changes are most commonly associated with cardiovascular systemic diseases or disorders ..., diabetes, or other ocular diseases corresponding to opthalmological disorders such as retinal degeneration" (page 164, lines 14-17).

Particular support for the amendments to claim 272, 273, 280 and 291 is found, for example, in the claims as originally filed; at page 63, line 26 to page 64, line 4; at pages 116-117; at page 162, line 19 to page 164, line 20; and elsewhere in the application as originally filed.

Support for the amendments to claim 273 is found, for example, at page 63, line 28; page 163,

line 22-23; and elsewhere in the application as originally filed.

Thus, Applicants submit that the application as originally filed provides clear support for the claimed subject matter.

These amendments are made without acquiescence to any rejections, and without prejudice to the prosecution of canceled subject matter in related divisional continuation, and continuation-in-part applications.

No new matter is added by way of the claim amendments.

Applicants note the withdrawal of the previous objections to claims 272 and 273 by the USPTO (pages 3 and 4 of the Office Action mailed August 18, 2010).

The Claim Objections and Rejections

Claim 272 stands objected to for alleged informalities.

Claim 273 stands objected to for allegedly not further limiting Claim 272 from which it depends.

Claims 272, 273, 280-284, and 291 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 272, 273, 280-284, and 291 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 272, 273, 280-284, and 291 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement, the USPTO suggesting that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully traverse the objections to the claims and the rejections to the claims.

The Objection to Claim 272

Claim 272 stands objected to for alleged informalities. However, as amended, the objections to Claim 272 for allegedly being informal are believed to be overcome.

The Objection to Claim 273

Claim 273 stands objected to as allegedly being of improper dependent form, the limitation "eye abnormality" recited in the claim allegedly not further limiting claim 272. However, as amended, Applicants believe that claim 273 further limits the subject matter of claim 272. Accordingly, Applicants submit that the objection of claim 273 is overcome.

The Rejections under 35 U.S.C. § 112, second paragraph

Claims 272, 273, 280-284, and 291 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite, the USPTO suggesting that Claim 272 includes both a broad range and a narrow range, and that inclusion of both ranges is considered indefinite.

However, Applicants note that Claim 272, as amended, no longer recites "a phenotype associated with a disruption of the gene that encodes for a native sequence PRO224 polypeptide" but instead is directed to a method of identifying an agent that modulates "an eye abnormality." Similarly, all the other claims, which all depend from Claim 272, are directed to methods of idenifying an agent that modulates an eye abnormality, so that the present claims recite "an eye abnormality" and do not recite "a phenotype." Thus, Claim 272 is believed to be definite under 35 U.S.C. § 112, second paragraph, and its dependent claims 273, 280-284, and 291 are believed to be definite under 35 U.S.C. § 112, second paragraph.

Accordingly, Applicants submit that the rejections of claims 272, 273, 280-284, and 291 under 35 U.S.C. § 112, second paragraph are overcome.

The Rejections under 35 U.S.C. § 112, first paragraph (possession)

Claims 272, 273, 280-284, and 291 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was

filed, had possession of the claimed invention.

Applicants respectfully traverse these rejections.

Applicants also note the acknowledgement by the USPTO that "Applicant was in possession of only the mouse DNA33221-1133 (UNQ198)" (page 9, line 5 of the final Office Action mailed August 18, 2010).

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. § 112, first paragraph is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." In re Kaslow, 707 F.2d 1366, 1375, 212 USPQ 1089, 1096 (Fed. Cir. 1983); see also Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See, e.g. Vas-Cath, 935 F.2d at 1563; 19 USPQ2d at 1116. The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Union Oil v. Atlantic Richfield Co., 208 F.3d 989, 996 (Fed. Cir. 2000).

Applicants note that the specification includes extensive and detailed description, including explicit disclosure of the amino acid sequence of PRO224 and nucleic acid sequence encoding for PRO224 (see, e.g., Figures 1 and 2, SEQ ID NO: 1, and SEQ ID NO: 2). The terms "knockout", "transgenic animal" and "abnormality," for example, are defined in the appliaction at pages 78 and 79. In addition, the application includes detailed teaching regarding the preparation of transgenic PRO224 knock-out mice recited in the claims (see, e.g., pages 116-117; pages 146-147; page 162, line 18 to page 164, line 2), the genome of which mice comprise a disruption of a gene which encodes for a PRO224 polypeptide (see, e.g., pages 146-147), and which mice exhibit characteristics and/or behavior which is described in detail in the application (see, e.g., pages 162-164), and which is related to diseases and disorders which are explicitly named in the application (see, e.g., page 13, lines 5-23; page 63, line 26 to page 64, line 4; and pages 162-164 of the application).

Accordingly, in view of the explicit recitation of PRO224 nucleic acid and amino acid

sequences, and of transgenic mice and the methods of preparing them, and of characteristics of transgenic mice whose genome comprises a disruption of a gene which encodes for a PRO224 polypeptide, Applicants respectfully submit that the disclosure of the application demonstrates extensive and sufficient identifying characteristics so as to convey to one of skill in the art that Applicants had possession of the claimed invention at that time the application was made. In particular, possession of the inventions of Claims 272, 273, 280-284, and 291, all of which recite or require a transgenic mouse comprising a disruption of a gene which encodes for a PRO224 polypeptide, is believed to be demonstrated by the disclosure of the application and claims as originally filed.

Accordingly, Applicants submit that the rejections of claims 272, 273, 280-284, and 291 under 35 U.S.C. § 112, first paragraph for alleged lack of written description sufficient to show possession of the claimed invention are overcome.

The Rejections under 35 U.S.C. § 112, first paragraph (enablement)

Claims 272, 273, 280-284, and 291 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement, the USPTO suggesting that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully traverse these rejections.

The enablement requirement of 35 U.S.C. § 112, first paragraph requires that the specification enable "those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation'." Genentech, Inc. v. Novo Nordisk, A/S 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)).

As amended, the present claims are directed to a method of identifying an agent that modulates a phenotype associated with a disruption of the gene that encodes for a native sequence PRO224 polypeptide, wherein said phenotype comprises an eye abnormality, and wherein the steps of the method utilize a transgenic mouse whose genome comprises a disruption of the gene which

encodes for the native sequence PRO224 polypeptide.

The USPTO was apparently concerned that the claimed methods included steps comprising "(a) providing any non-human transgenic mammal ..." (page 12, line 16 of the final Office action mailed August 18, 2010). However, Applicants note that the present claims do not recite "non-human transgenic mammal" but instead recite "transgenic mouse." The USPTO was also concerned that a non-human mammal might not include a human gene (e.g., page 13, line 10 of the final Office action mailed August 18, 2010), and that generation of a non-human transgenic animal might be unpredictable (e.g., page 14, lines 3-4 of the final Office action mailed August 18, 2010). However, the present claims are directed to methods which require transgenic mice, as produced by the Applicants and as disclosed and taught in the present application.

For example, Applicants note that the specification provides detailed and specific teaching regarding the production of transgenic mice suitable for use in the claimed methods. For example, the application teaches the nucleotide and amino acid sequences of PRO224 molecules (see, e.g., page 46 and Figures 1 and 2) and identifies a cDNA clone that has been deposited with ATCC (ATCC 209263, deposited September 16, 1997 (see page 145, line 16)). The application provides detailed teaching regarding producing transgenic mice having a disruption in a gene encoding for PRO224 polypeptide, and explicit examples of such transgenic mice (see, for example, page 116, line 21 to page 117, line 21; page 146, line 7 to page 147, line 11; page 163, line 14 to page165, line 14; and elsewhere in the application). Thus, particular sequences, SEQ ID NO: 1 and SEQ ID NO: 2, are disclosed in the application. In addition, Applicants note that the methods recite transgenic mice comprising a disruption of the gene that encodes for a native sequence PRO224 polypeptide, which sequences are provided; that the claimed methods require knock-out mice with a phenotype comprising an eye abnormality, as disclosed in the application; and that methods for generating such knock-out mice, and for measuring eye abnormalities, are also taught in the application. Thus, Applicants submit that the teaching of the application is detailed and specific, and is sufficient to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation.

In addition, the claims define the association between the physiological characteristics measured in the eyes of transgenic and wild-type mice and eye abnormalities:

"(c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type mouse, wherein the physiological characteristic of an eye of the transgenic mouse that differs from the physiological characteristic of the wild-type mouse is identified as an eye abnormality resulting from the gene disruption in the transgenic mouse;"

and thus one of skill in the art is enabled to make the comparison recited in the claims.

Citing Upton *et al.*, the USPTO is concerned that there allegedly may not be a "clear association" between a phenotype of a retinal abnormality and a physiological characteristic of increased mean artery-to-vein ratio (page 17, lines 9-12 of the final Office action maield August 18, 2010). However, Applicants note that Upton *et al.* did not investigate **retinal abnormalities**, but instead is directed to measurements of axonal projections in **brainstem nuclei** (superior colliculus and lateral geniculate) originating from the retinal ganglion cells in knock-out mice as compared to wild type mice. **The superior colliculus and the lateral geniculate are not in the eye; they are located in the brainstem**. Thus, although axonal projections to the superior colliculus and the lateral geniculate are clearly of importance to vision, it is not clear how the Upton *et al.* might relate to a phenotype of *eye abnormality*, nor to a physiological characteristic of increased mean artery-to-vein ratio. As Upton *et al.* do not discuss retinal abnormalities, it is unclear how Upton *et al.* relates to the present claimed invention.

More particularly, Applicants disclose the results of the ophthalmologic measurements (A/V ratio determined from optic fundus photography and angiography) taken from wild-type and knock-out mice having a disruption of the gene encoding PRO224, disclose that these results show differences between the wild-type and knock-out mice, and disclose that an abnormal A/V ratio is indicative of diseases or disorders such as ocular diseases corresponding to ophthalmologic disorders (page 163, lines 29-21). In addition, Applicants note that the results disclosed the present application demonstrate a difference in the mean artery-to-vein ratio *in the retinas* of knock-out mice as compared to gender-matched control wild-type mice. These observed differences therefore show that the retinas of knock-out mice are abnormal as compared to normal control mice. Thus, *by definition*, the observed differences are **retinal abnormalities** in the knock-out mice.

Thus, the disclosed measurements of artery and vein dimensions or properties, in the retina, which differ between knock-out and wild type mice, demonstrate that the PRO224 knock-out mice described in the present application exhibit *eye abnormalities*, since the eyes of the knock-out mice differ from the eyes of wild-type mice. Thus, Applicants believe the USPTO's concerns regarding the association between retinal abnormality and increased mean artery-to-vein ratio are overcome.

The USPTO further expressed concern that the steps of claim 272 might refer to "two distinct scopes of phenotypes" (page 17, line 19). However, as amended, claim 272 no longer refers to phenotypes; thus, this concern is believed to be moot.

On page 18 of the instant Office Action, the USPTO again suggests that allegedly "the phenotype of transgenic animal, including transgenic mouse, is unpredictable," citing Matthaei (page 18, lines 1-2 of the instant Office Action). Applicants note that the present claims, as amended, do not refer to a "phenotype" so that any concern regarding an allegedly unpredictable phenotype is believed to be moot.

However, even in view of the possible concerns raised by the USPTO, Applicants note that the present claimed invention is directed to methods which include an internal control, e.g., require comparison of knock-out and wild-type mice, as required in the claims and as disclosed in the examples of the application, so that the required elements of the comparing steps of the claimed methods take care of, and avoid, any possible "unpredictability"; thus, any possible "unpredictability" is believed not to be a concern. In addition, Applicants note that the present methods are directed to methods using knock-out mice having an eye abnormality; thus, even if there were to be any "unpredictability" in the production of knock-out mice, the methods require comparison of these mice with wild-type control mice, and the methods are thus quite adequate and predictable for identifying an agent which modulates an eye abnormality. Accordingly, Applicants submit that the concerns regarding subjects discussed by Matthaei are overcome.

Applicants respectfully submit that the claims are directed to methods of identifying agents that modulate the disclosed eye abnormalities (e.g., the disclosed characteristics) of the transgenic mouse disclosed in the application. The present claims do not refer to, and do

not depend upon, a "phenotype" but instead are directed to identification of an agent that modulates an eye abnormality. However, Applicants submit that the USPTO's concerns are overcome by the disclosure of the application, the knowledge and skill of one of ordinary skill in the art, and in view of the present claim amendments. Accordingly, Applicants submit that the claimed methods are enabled by the specification.

Accordingly, Applicants submit that the rejections of claims 272, 273, 280-284, and 291 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement are overcome.

CONCLUSION

Applicants believe that the present application is in *prima facie* condition for allowance; accordingly, speedy notice of their allowance is respectfully requested.

Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **50-2387** (referencing Attorney's **Docket No. GNE-5201 R1 (24126-286)**.

Respectfully submitted,

Date: October 29, 2010

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